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Description

Preparations for the treatment of rosacea

The invention relates to topical cosmetic or dermatological preparations which are suitable for the treatment of rosacea. Here, rosacea also includes the symptoms of couperose.

Rosacea is an inflammatory disease, mainly of the face, which is accompanied with marked erythema, which lasts for a varying length of time, papules and pustules. Telangiectasis and elastosis are frequent, and the intrafollicular accumulation of neutrophils is also observed. Rosacea patients have skin which is extremely sensitive to chemical toxins and physical stress factors (UV light). The pathogenesis is unclear.

Rosacea is incurable, but can be treated with antibiotics, isotretinoin, fungicides such as metronidazole or betablockers.

In contrast to many skin diseases which are associated with a massive influx of leucocytes, leucocyte infiltration in the vicinity of blood vessels and sebaceous glands is moderate.

The question of whether the difficult-to-treat erythema in rosacea patients could be reduced using NO-synthase inhibitors has already been raised in the literature (Qureshi, A.A. et al; Arch. Dermatol. Vol. 132, Aug. 1996, 889-893). An answer, however, has not been given.

Only in the advanced stages of rosacea do telangiectases, papules, pustules and growths such as rhinophyma appear in addition to the differingly developed erythena. These symptoms are treated using surgery.

Overall, the success of the pharmacological treatment of rosacea is unsatisfactory.

The object of the invention was therefore to provide a remedy in this respect and, in particular, to provide active ingredients and preparations with which rosacea, in particular the early stages of this disease, can be treated safely and free from side effects.

These objects are achieved according to the invention.

The invention provides the use, in particular topical use, of one compound or two or more compounds chosen from the group of NO-synthase inhibitors and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

The invention also provides the use of cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group of NO-synthase inhibitors and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

The invention further provides cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group of NO-synthase inhibitors and derivatives thereof.

Suitable NO-synthase inhibitors are, for example,
2-iminobiotin,
L-N^5-(1-iminoethyl)-ornithine (L-NIO),
S-methylisothiourea
S-methylisothiourea sulphate (SMT),
S-methyl-L-thiocitrulline,
L-N^G-(1-iminoethyl)lysine (L-NIL),
7-nitroindazole (7-Ni),
S,S'-1,3-phenylenebis(1,2-ethanediyl)bisisothiourea (NITU)
L-thiocitrulline (2-thioureido-L-norvaline)
and derivatives thereof and, in particular, arginine derivatives.

Preference is given to NO-synthase inhibitors which contain a guanidine group.

Suitable derivatives are, for example, the compounds according to the invention which are monoalkylated or dialkylated on the imino groups or amino groups.

In each case, the alkyl radicals of the monoalkyl groups or dialkyl groups can have from 1 to 10, preferably from 1 to 6, but in particular 1, 2 or 3, carbon atoms, and can be straight-chain or branched.

Also highly suitable are derivatives, in particular of arginine, whose amino groups are completely or partially acylated. These are, in particular, the amino groups of the amino acid radical and, in particular, the amino groups bonded to the alpha-carbon atom. Preference is given to the monoacyl compounds of the active ingredient according to the invention, in particular of an arginine derivative.

A preferred acyl radical is alkylcarbonyl, which is obtained in acylations with carboxylic acids or derivatives thereof, e.g. acid chlorides or anhydrides. The acyl radical or alkylcarbonyl radical can have 2-12, in particular 2-6, carbon atoms and is particularly preferably acetyl.

The compound alpha-N-acetyl-N^G-nitro-L-arginine methyl ester (alpha-N-acetyl-L-NAME), in which the amino group of the alpha-carbon atom of the amino acid function is monoacetylated, is particularly preferred.

The acyl derivatives are characterized by good effectiveness, storage stability and their stability in preparations.

Suitable derivatives of the compounds according to the invention are, in particular, the salts and acid addition salts. Esters of carboxylic acid groups of the compounds according to the invention with alcohols are also preferred.

Preferred salts are water-soluble salts, e.g. sodium, potassium and ammonium salts. This is also true for the acid addition salts. Suitable acid addition salts are, for example, obtained using inorganic and organic acids. Preference is given to the hydrochlorides, phosphates, sulphates, acetates, caprylates, citrates, lactates, maleates or tartrates.

Suitable esters are, for example, those formed with short-chain or medium-chain alcohols, preferably with monoalcohols. They can be straight-chain or

branched and have, for example, from 1 to 12, preferably from 1 to 6, carbon atoms. Preference is given to methanol, ethanol, n-propanol and isopropanol.

The esters are particularly preferred derivatives. They are also characterized by better penetration.

The compounds according to the invention are known per se, available commercially or can be obtained by known processes. The literature describes their effect as NO-synthase inhibitors. The acylated compounds can be obtained using the known acylating process.

Particular preference is given to NO-synthase inhibitors according to the invention which contain an arginine radical, and derivatives thereof, in particular as described below.

The invention thus provides in particular for the use, in particular topical use, of one compound or two or more compounds chosen from the group of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

The invention also provides in particular for the use of cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof for the prophylaxis and/or treatment of rosacea and couperose.

The invention further provides cosmetic or dermatological topical preparations with a content of one compound or two or more compounds chosen from the group of N^G-monoalkyl-L-arginine, N^G, N^G-dialkyl-L-arginine, N^G, $N^{G'}$-dialkyl-L-arginine and N^G-nitro-L-arginine and derivatives thereof.

In each case, the alkyl radicals of the monoalkyl groups or dialkyl groups can have from 1 to 10, preferably from 1 to 6, but in particular 1, 2 or 3, carbon atoms, and can be straight-chain or branched.

Suitable derivatives of the compounds according to the invention are, in particular, the salts and acid addition salts. Esters of the carboxylic acid group of the arginine with alcohols are also preferred.

Preferred salts are water-soluble salts, e.g. sodium, potassium and ammonium salts. This is also true for the acid addition salts. Suitable acid addition salts are, for example, obtained using inorganic and organic acids. Preference is given to the hydrochlorides, phosphates, sulphates, acetates, caprylates, citrates, lactates, maleates or tartrates.

Suitable esters are, for example, those formed with short-chain or medium-chain alcohols, preferably with monoalcohols. They can be straight-chain or branched and have, for example, from 1 to 12, preferably from 1 to 6, carbon atoms. Preference is given to methanol, ethanol, n-propanol and isopropanol.

The esters are particularly preferred derivatives. They are also characterized by better penetration.

These compounds according to the invention are also known, available commercially or can be obtained by known processes. The literature describes their effect as NO-synthase inhibitors.

Preference is given to the following compounds:
N^G-monomethyl-L-arginine,
N^G-monoethyl-L-arginine,
N^G-nitro-L-arginine,
N^G-nitro-L-arginine methyl ester,
N^G-nitro-L-arginine ethyl ester,
N^G-monomethyl-L-arginine methyl ester,
N^G-monoethyl-L-arginine methyl ester,
N^G-monomethyl-L-arginine ethyl ester
N^G-monoethyl-L-arginine ethyl ester and
N^G, N^G-dimethyl-L-arginine,
N^G, $N^{G'}$-dimethyl-arginine,
N^G, N^G-dimethyl-L-arginine dihydrochloride,
N^G, $N^{G'}$-dimethyl-L-arginine dihydrochloride.

Particular preference is given to the following compounds:
N^G-monomethyl-L-arginine monoacetate (L-NMMA),

N^G-monoethyl-L-arginine monoacetate (L-MEA),
N^G-nitro-L-arginine (L-NNA) and
N^G-Nitro-L-arginine methyl ester hydrochloride (L-NAME).
N^G-nitro-L-arginine methyl ester or
L-NAME is very particularly preferred.

The dermatological and cosmetic topical preparations according to the invention can comprise, as active ingredient, one NO-synthase inhibitor or two or more NO-synthase inhibitors, e.g. one, two or three compounds.

If the preparations comprise two or more of the active ingredients according to the invention, particular preference is given to those preparations which comprise at least one NO-synthase inhibitor containing an arginine radical, in particular one of the abovementioned active ingredients containing an arginine radical.

Particular preference is given to those active ingredient combinations and preparations therewith which contain L-NAME and/or L-NMMA.

The active ingredients which contain an arginine radical can be present in the combinations, for example, in amounts of 10-90% by weight, in particular 30-70% by weight, in each case based on the total weight of the active ingredients.

The compounds according to the invention and the dermatological and cosmetic topical preparations therewith are highly suitable for the treatment and prophylactic treatment of cuperose and of rosacea, in particular of stages I or II.

Surprisingly, the active ingredients and preparations according to the invention exhibit a long-lasting, continuous effect during application. Even after treatment has finished, the skin remains symptom-free and considerably improved for a long time, for example for a period of several weeks.

The cosmetic or dermatological topical preparations according to the invention may be based on formulation bases which are customary per se and serve for the treatment of skin in the sense of a dermatological treatment or a treatment in the cosmetic sense.

The in particular topical use according to the invention of the NO-synthase inhibitors surprisingly leads to a reduction in the cutaneous bloodflow and thus of the erythema. The thereby increased infiltration of leucocytes and other immune cells leads to better healing of the inflamed tissue.

The objects presented are thus achieved.

The active ingredients according to the invention and/or their derivatives are preferably present in the topical cosmetic or dermatological preparations according to the invention in amounts of from 0.001 to 20% by weight, particularly preferably from 0.01 to 10% by weight, but in particular from 0.1 to 5% by weight, in each case based on the total preparation.

Surprisingly, the symptoms of rosacea, in particular the erythema, are alleviated or avoided according to the invention.

Particularly advantageous preparations are also obtained if the active ingredients according to the invention are combined with antioxidants.

The antioxidants according to the invention can be chosen advantageously from the group of customary cosmetic or dermatological antioxidants, in particular from the group consisting of tocopherols and derivatives thereof, particularly α-tocopherol or α-tocopheryl esters, in particular α-tocopheryl acetate, and also sesamol, gallic acid derivatives, such as methyl, ethyl, propyl, amyl, butyl and lauryl gallate, the konyferyl benzoate of benzoin resin, nordihydroguaiac resin acid, nordihydroguaiaretic acid, butylhydroxyanisole, butylhydroxytoluene, ascorbic acid, citric acid, phosphoric acid, lecithin, trihydroxybutyrophenone, carotenes, vitamin A and derivatives thereof, in particular retinyl palmitate, ascorbic acid, ascorbyl palmitate, dilauryl thiodipropionate, distearyl thiodipropionate, monoisopropyl citrate, thiodipropionic acid, EDTA and EDTA derivatives, cysteine, glutathione and esters, uric acid, lipoic acid and esters, carotenes, heavy metal complexing agents such as delta-aminolaevulinic acid and phytic acid and Desferral® (Ciba-Geigy) and flavonoids, e.g. 4^{G}-alpha-glucopyranosyl-rutin.

The cosmetic or dermatological preparations according to the invention preferably comprise from 0.01 to 10% by weight, but in particular from 0.1 to 6% by weight, based on the total weight of the preparations, of one or more substances from the group of antioxidants.

It is preferable to choose the antioxidants according to the invention from the group of flavonoids or of tocopherols and derivatives thereof.

For use, the preparations are applied to the skin in a sufficient amount once or several times daily in the manner customary for cosmetics or dermatological agents.

Particular preference is given to skincare preparations and sunscreen preparations.

Dermatological and cosmetic preparations according to the invention can be in various forms. Thus, for example, aqueous, alcoholic or aqueous-alcoholic solutions, emulsions of the oil-in-water type (O/W), emulsions of the water-in-oil type (W/O), multiple emulsions, e.g. of the water-in-oil-in-water type (W/O/W), gels, hydrodispersions, solid sticks or aerosols can comprise the aforementioned active ingredient combinations. Preference is also given to low-water or water-free ointments and preparations.

The topical preparations according to the invention can comprise customary auxiliaries such as emulsifiers and preservatives.

Preference is also given to those cosmetic and dermatological preparations which are in the form of a sunscreen. Advantageously, these additionally comprise at least one UVA filter and/or at least one UVB filter and/or at least one inorganic pigment. Particular preference is given to preparations containing one or more UVA filters. Particular preference is given to UVA filters with strong absorption at 340 nm.

However, advantageous preparations are also those which are applied to the skin following exposure to sunlight, i.e. aftersun products. In the case of such preparations, the person skilled in the art must use his discretion as to whether additional UV filter substances should be used or not.

Cosmetic preparations according to the invention for the protection of the skin against UV rays can be in various forms, as are, for example, customarily used for this type of preparations. Thus, for example, they can be aqueous, alcoholic or aqueous-alcoholic solutions, emulsions of the water-in-oil type (W/O) or of the oil-in-water type (O/W), or multiple emulsions, for example of the water-in-

oil-in-water type (W/O/W), gels, hydrodispersions, oils, solid sticks or else aerosols.

The topical preparations according to the invention can comprise dermatological and cosmetic auxiliaries, as are customarily used in such preparations, e.g. preservatives, bactericides, perfumes, antifoams, dyes, pigments which have a colouring effect, thickeners, surface-active substances, emulsifiers, emollients, moisturizers and/or humectants, fats, oils, waxes, or other customary constituents of a cosmetic formulation such as alcohols, polyols, polymers, foam stabilizers, electrolytes, organic solvents or silicone derivatives.

If the cosmetic or dermatological preparation is a solution or lotion, the solvents used may be:

- water or aqueous solutions;

- oils, such as triglycerides of capric or of caprylic acid, but preferably castor oil;

- fats, waxes and other natural and synthetic fatty substances, preferably esters of fatty acids with alcohols of low carbon number, e.g. with isopropanol, propylene glycol or glycerol, or esters of fatty alcohols with alkanoic acids of low carbon number or with fatty acids;

- alcohols, diols or polyols of low carbon number, and ethers thereof, preferably ethanol, isopropanol, propylene glycol, glycerol, ethylene glycol, ethylene glycol monoethyl or monobutyl ether, propylene glycol monomethyl, monoethyl or monobutyl ether, diethylene glycol monomethyl or monoethyl ether and analogous products.

In particular, mixtures of the abovementioned solvents are used. In the case of alcoholic solvents, water can be an additional constituent.

Oils or emulsions according to the invention, for example in the form of a sunscreen cream, a sunscreen lotion or a sunscreen milk, are advantageous and comprise, for example, the specified fats, oils, waxes and other fatty substances, and water and an emulsifier, as is customarily used for this type of formulation.

Cosmetic and dermatological preparations for the treatment and care of the skin can be in the form of gels which, in addition to the active ingredients and the solvents customarily used therefor, also comprise organic thickeners, e.g. gum arabic, xanthan gum, sodium alginate, cellulose derivatives, preferably methylcellulose, hydroxymethylcellulose, hydroxyethylcellulose, hydroxypropylcellulose, hydroxypropylmethylcellulose, or inorganic thickeners, e.g. aluminium silicates such as, for example, bentonites, or a mixture of polyethylene glycol and polyethylene glycol stearate or distearate. The thickener is present in the gel, for example, in an amount between 0.1 and 30% by weight, preferably between 0.5 and 15% by weight.

Gels according to the invention usually comprise alcohols of low carbon number, e.g. ethanol, isopropanol, 1,2-propanediol, glycerol and water, or an abovementioned oil in the presence of a thickener which, in the case of oily-alcoholic gels, is preferably silicon dioxide or an aluminium silicate, and in the case of aqueous-alcoholic or alcoholic gels, is preferably a polyacrylate.

Hydrodispersions are dispersions of a liquid, semisolid or solid inner (discontinuous) lipid phase in an outer aqueous (continuous) phase.

In contrast to O/W emulsions, which are characterized by a similar phase arrangement, hydrodispersions are, however, essentially free from emulsifiers. Hydrodispersions, like emulsions, are metastable systems and have a propensity to convert to a state of two coherent discrete phases. In emulsions, the choice of a suitable emulsifier prevents phase separation.

In the case of hydrodispersions of a liquid lipid phase in an outer aqueous phase, the stability of such a system can, for example, be ensured by building up a gel structure in the aqueous phase, in which structure the lipid droplets are suspended in stable form.

Solid sticks according to the invention can, for example, comprise natural or synthetic waxes, fatty alcohols or fatty acid esters. Preference is given to lipcare sticks.

Suitable propellants for cosmetic or dermatological preparations which can be sprayed from aerosol containers are the customary known readily volatile, liquefied propellants, for example hydrocarbons (propane, butane, isobutane),

which can be used alone or mixed with one another. Compressed air can also be used advantageously.

The person skilled in the art is of course aware that there are propellants which are nontoxic per se which would in principle be suitable for the present invention, but which should nevertheless be avoided because of an unacceptable impact on the environment or other accompanying circumstances, in particular fluorinated hydrocarbons and fluorochlorocarbons (CFCs).

Preferably, the preparations according to the invention can also comprise substances which absorb UV radiation in the UVB region, the total amount of filter substances being, for example, from 0.1% by weight to 30% by weight, preferably from 0.5 to 10% by weight, in particular from 1 to 6% by weight, based on the total weight of the preparation, in order to make available preparations which protect the skin against the entire range of ultraviolet radiation. They can also serve as sunscreens.

The UVB filters can be oil-soluble or water-soluble. Examples of oil-soluble substances are:

- 3-benzylidenecamphor derivatives, preferably
  3-(4-methylbenzylidene)camphor, 3-benzylidenecamphor;

- 4-aminobenzoic acid derivatives, preferably
  2-ethylhexyl 4-(dimethylamino) benzoate,
  amyl 4-(dimethylamino)benzoate;

- esters of cinnamic acid, preferably
  2-ethylhexyl 4-methoxycinnamate,
  isopentyl 4-methoxycinnamate;

- esters of salicylic acid, preferably
  2-ethylhexyl salicylate,
  4-isopropylbenzyl salicylate,
  homomenthyl salicylate;

- derivatives of benzophenone, preferably
  2-hydroxy-4-methoxybenzophenone,

2-hydroxy-4-methoxy-4'-methylbenzophenone,
2,2'-dihydroxy-4-methoxybenzophenone;

- esters of benzalmalonic acid, preferably
di(2-ethylhexyl) 4-methoxybenzalmalonate;

- 2,4,6-trianilino(p-carbo-2'-ethyl-1'-hexyloxy)-1,3,5-triazine.

Examples of water-soluble substances are:

- salts of 2-phenylbenzimidazole-5-sulphonic acid such as its sodium, potassium or triethanolammonium salt,
and the sulphonic acid itself;

- sulphonic acid derivatives of benzophenones, preferably
2-hydroxy-4-methoxybenzophenone-5-sulphonic acid and its salts;

- sulphonic acid derivatives of 3-benzylidenecamphor, such as
e.g. 4-(2-oxo-3-bornylidenemethyl)benzenesulphonic acid,
2-methyl-5-(2-oxo-3-bornylidenemethyl)sulphonic acid and its salts.

The invention also provides the combination of active ingredients according to the invention with one or more UVA and/or UVB filters, and cosmetic or dermatological preparations according to the invention which also comprise one or more UVA and/or UVB filters.

It can also be particularly advantageous to combine the active ingredients with UVA filters which are customarily present in cosmetic and/or dermatological preparations. The substances are preferably derivatives of dibenzoylmethane, in particular 1-(4'-tert-butylphenyl)-3-(4'-methoxyphenyl)propane-1,3-dione and 1-phenyl-3-(4'-isopropylphenyl)propane-1,3-dione. These combinations and preparations which comprise these combinations are also provided by the invention. The amounts which can be used are those given for the UVB combination.

Advantageous preparations are also obtained if the active ingredients according to the invention are combined with UVA and UVB filters.

Combinations of the active ingredients according to the invention with one or more antioxidants and one or more UVA filters and/or one or more UVB filters are also particularly advantageous according to the invention.

The cosmetic or dermatological preparations can also comprise inorganic pigments which are customarily used in cosmetics for protecting the skin against UV rays. These are oxides of titanium, zinc, iron, zirconium, silicon, manganese, aluminium, cerium and mixtures thereof, and modifications in which the oxides are the active agents. Particularly preferably, they are pigments based on titanium dioxide.

The invention also provides the process for the preparation of the topical preparations according to the invention, which is characterized in that the active ingredients are incorporated into cosmetic or dermatological formulations in a manner known per se.

All quantities, proportions and percentages are, unless stated otherwise, based on the weight and the total amount or on the total weight of the preparations.

The examples below serve to illustrate the present invention without limiting it.

In the examples, the following compounds are used:

N^G-monomethyl-L-arginine monoacetate (L-NMMA),
N^G-monoethyl-L-arginine monoacetate (L-MEA),
N^G-nitro-L-arginine (L-NNA),
N^G-nitro-L-arginine methyl ester hydrochloride (L-NAME).

Example 1

Sun gel (transparent)

	% by weight
L-NAME	1
Benzophenone-4	0.5
Phenylbenzimidazolesulphonic acid	1.3
Acrylamide/sodium acrylate copolymer	1.6
Ethanol	5.0
Glycerol	15.0
NaOH (15% strength)	q.s.
Perfume, preservative	q.s.
Water, demin. (demineralized)	ad 100.0

Example 2

Hydrodispersion

	% by weight
L-NMMA	5.0
Phenyltrimethicone	1.0
Carbomer (Carbopol 981)	1.0
Hydroxypropylmethylcellulose	0.2
Butylene glycol	3.0
Tromethamine	q.s.
EDTA solution (14% strength)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 3

O/W sun milk

	% by weight
L-MEA	2.5
Urea	5.0
Octyl methoxycinnamate	5.0
Butylmethoxydibenzoylmethane	1.0
Cetearyl alcohol + PEG-40 castor oil + sodium cetearyl sulphate	2.5
Glyceryl lanolate	1.0
Laurylmethicone copolyol	0.5
Mineral oil (GP 9)	5.0
Caprylic/capric triglycerides	5.0
Acrylamide-sodium acrylate copolymer	0.3
Cyclomethicone	2.0
TiO_2	1.0
Glycerol	3.0
EDTA solution (14% strength)	0.5
Ethanol	5.0
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 4

W/O care lotion

	% by weight
L-NNA, HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 5

O/W face-care cream

	% by weight
L-NMMA	2.5
PEG-5 glyceryl stearate	2.00
Glyceryl stearate	3.00
Cyclomethicone	3.00
Caprylic/capric triglycerides	3.00
Cetyl alcohol	3.00
Ethanol	1.00
Hyaluronic acid	0.05
Tocopheryl acetate	0.50
Glycerol	4.00
Perfume, preservative	q.s.
Water, demin.	ad 100.00

Example 6

W/O cream

	% by weight
L-NMMA	2.5
PEG-22 dodecyl glycol copolymer	3.0
Cetyl dimethicone copolyol	2.0
Cyclomethicone	4.0
Mineral oil (GP 9)	4.0
Caprylic/capric triglycerides	4.0
Glycerol	4.00
Perfume, preservative	q.s.
Water, demin.	ad 100.00

Example 7

Aftersun lotion

	% by weight
L-NAME	5.0
Cetearyl alcohol + PEG-40 castor oil + sodium cetearyl sulphate	2.50
Glyceryl stearate SE	0.60
Mineral oil (GP 9)	4.00
Caprylic/capric triglycerides	2.00
Shea butter	2.00
Avocado oil	2.00
Tocopheryl acetate	3.00
Acrylamide-sodium acrylate copolymer	0.30
Glycerol	4.00
Hyaluronic acid	0.05
Bisabolol	0.05
Perfume, preservative	q.s.
Water, demin.	ad 100.00

Example 8

Shower milk

	% by weight
L-MEA	5.0
Sodium laureth sulphate	11
Cocamidopropyl betaine	5
Cocamide DEA	1
PEG-8	1
Soybean oil	1
Citric acid	0.1
Sodium chloride	0.2
Fragrance	0.1
Water, demin.	ad 100.00

Example 9

Care stick

	% by weight
1,2-Propylene glycol	11.0
Oleyl alcohol	14.0
Eosin dyes	3.0
Stearamide MEA (Rewomid S 280)	10.0
Beeswax	10.0
Glycerol monostearate	10.0
Cetyl alcohol	10.0
Ceresine	8.0
Stearyl heptanoate (CL-solid)	6.0
Lanolin anhydr.	6.0
Pigments and coloured lakes	6.0
Perfume oil	1.0
L-NAME	5.0

Example 10

Stick

	% by weight
Castor oil (and) glyceryl ricinoleate (and) octyldodecanol (and) carnauba (and) candelilla wax (and) microcrystalline (and) cetyl alcohol (and) beeswax (and) mineral oil	
Cutina LM (Henkel)	65
Caprylic/capric triglycerides (Myristol 318)	20
Pigment colours	3.0
Titanium dioxide	7.0
L-NMMA	4.0
L-NIO	1.0

Example 11

Stick

	% by weight
Castor oil (and) glyceryl ricinoleate (and) octyldodecanol (and) carnauba (and) candelilla wax (and) microcrystalline wax (and) cetyl alcohol (and) beeswax (and) mineral oil Cutina LM (Henkel)	78.0
Octyldodecanol (Eutanol G)	15.0
Colour pigments	2.0
L-NMMA	4.0
L-NIL	1.0

Example 12

W/O care lotion

	% by weight
2-Iminobiotin	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 13

W/O care lotion

	% by weight
L-NIO-HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 14

W/O care lotion

	% by weight
S-Methylisothiourea sulphate	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 15

W/O care lotion

	% by weight
S-Methyl-L-thiocitrulline 2HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 16

W/O care lotion

	% by weight
L-NIL-2HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 17

W/O Care lotion

	% by weight
7-Nitroindazole	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 18

W/O Care lotion

	% by weight
PBITU-2HBr	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 19

W/O Care lotion

	% by weight
L-Thiocitrulline 2HCl	2.5
Cyclomethicone	3.0
PEG-1 glycerol sorbitan oleostearate	1.7
PEG-7 hydrogenated castor oil	6.3
Mineral oil (GP 9)	13.0
Caprylic/capric triglycerides	13.0
Glycerol	4.0
$MgSO_4$	0.7
Perfume, preservative	q.s.
Water, demin.	ad 100.0

Example 20

Sun gel (transparent)

	% by weight
Alpha-N-acetyl-L-NAME (with monoacetylated amino group on the alpha-carbon atom of L-NAME)	1
Benzophenone-4	0.5
Phenylbenzimidazolesulphonic acid	1.3
Acrylamide/sodium acrylate copolymer	1.6
Ethanol	5.0
Glycerol	15.0
NaOH (15% strength)	q.s.
Perfume, preservative	q.s.
Water, demin. (demineralized)	ad 100.0

Example 21

Preparation of alpha-N-acetyl-L-NAME (in accordance with Example 20)

1 equivalent of L-NAME hydrochloride is dissolved in methanol/Na methoxide (1 equivalent, 8 ml of methanol/mmol) under nitrogen and stirred with 1.5 equivalents of acetic anhydride for 2 h. It is then worked up as usual under aqueous conditions and admixed with saturated NaCl solution and extracted with ethyl acetate and dried with Mg sulphate. The solvent is stripped off to give pure alpha-N-acetyl-L-NAME, yield 71%.

^{1}H-NMR spectrum: 1.60, multiplet, 4 H; 1.90, singulet, 3 H; 3.15, triplet, 2 H; 3.60, singulet, 3H of the acetyl-Me group; 4.35, triplet, 1 H.

alpha-N-Acetyl-N^G-monomethyl-L-arginine monoacetate (alpha-N-acetyl-L-NMMA),
alpha-N-acetyl-N^G-monoethyl-L-arginine monoacetate (alpha-N-acetyl-L-MEA),
alpha-N-acetyl-N^G-nitro-L-arginine (alpha-N-acetyl-L-NNA),
alpha-N-acetyl-N^G-nitro-L-arginine methyl ester (alpha-N-acetyl-L-NAME) are obtained in an analogous way.

The N-acyl compounds according to the invention of the NO-synthase inhibitors which optionally carry one or more amino groups or a guanidine group are novel, in particular the acetyl compounds, e.g. the monoacetyl compounds, in particular those acyl compounds or acetyl compounds of amino groups or alpha-carbon amino groups of amino acids. Further preferred acyl radicals are aromatically substituted carbonyl, for example benzoyl.

Acyl compounds according to the invention are obtained by customary acylation processes, e.g. by reaction of [lacuna] with acid halides or acid anhydrides, optionally with the addition of solvents and bases, e.g. triethylamine or alkoxides. For the monoacyl compounds, equivalent amounts of NO-synthase inhibitors and acylating agents are preferred. For polyacylated compounds, for example, correspondingly higher equivalent amounts are used, it being possible, for example, where appropriate, to react other amino groups and the guanidino group.